August 24, 2020

Administrator Andrew Wheeler
Dr. Kris Thayer, Director, Chemical and Pollutant Assessment Division, ORD
U.S. Environmental Protection Agency

Comment filed via regulations.gov

Comment regarding: Notice of Public Comment Period on Technical Documents for External Peer Review and the Pool of Candidate Peer Reviewers for a Report on Physiologically Based Pharmacokinetic (PBPK) Modeling for Chloroprene and a Supplemental Analysis of Metabolite Clearance, 85 Fed. Reg. 44,885 (July 24, 2020), Docket: EPA-HQ-ORD-2020-0181-0001

Dear Administrator Wheeler and Dr. Thayer:

In November 2019, a coalition of scientists, affected community members, and advocates met with EPA, citing concern that EPA may be engaging in or considering a process that is out of step with its own IRIS protocol and guidelines. The sudden and surprising review of industry's requested model now only adds confusion and delay – when EPA should simply, once again, reaffirm the 2010 IRIS value for Chloroprene. The undersigned Commenters call on EPA not to take a course that would represent an erosion of the integrity of the science assessments EPA's research staff conducts and the science-based actions that communities rely on for protection.

Residents of LaPlace, Louisiana first became aware of elevated air pollution after the 2011 National Air Toxics Assessment (NATA) showed cancer risks that are as high as 826-in-1 million for this community.[1] The most recent NATA, released in 2018 and utilizing data from 2014, found that cancer risks in this community are as high as 1505-in-1 million, driven primarily by chloroprene emissions emitted by Denka Performance Elastomer (DPE), and ethylene oxide emissions from another nearby facility.[2] Based on EPA's most current data, the parishes of St. John the Baptist and St. Charles have the census tracts with the highest cancer risk in the United States.

Yet to date, EPA has met with affected community members to discuss current actions under the Information Quality Guidelines once. EPA communicated with residents living near the Denka facility that it is undertaking the current actions; however, EPA did not communicate with meeting attendees and instead, Commenters became aware of the current actions via a public Federal Register Notice.[3] While the comment period for this review process opened on

[1] EPA, EPA in Louisiana – LaPlace, Louisiana Background Information (2016), https://www.epa.gov/la/laplace-louisiana-background-information.
[2] EPA, 2014 National Air Toxics Assessment (2018), https://www.epa.gov/national-air-toxics-assessment/2014-nata-assessment-results; Sharon Lerner, A Tale of Two Toxic Cities, The Intercept (Feb. 24, 2019), https://theintercept.com/2019/02/24/epa-response-air-pollution-crisis-toxic-racial-divide/ at Table: 109 Air Pollution Hotspots.
[3] Notice of Public Comment Period on Technical Documents for External Peer Review and the Pool of Candidate Peer Reviewers for a Report on Physiologically Based Pharmacokinetic (PBPK) Modeling for Chloroprene and a

July 24, 2020, key supplemental and supporting documents were posted to the regulations.gov website six days later, which denied Commenters the ability to have a full 30- day review.

The current actions outlined in the "Background Description for Chloroprene PBPK Modeling"[4] raise concerns that EPA plans to reevaluate the established chloroprene cancer risk value or inhalation unit risk factor (IUR) based on a single study commissioned by the sole regulated entity in the United States. Furthermore, existing agency documentation suggests that the PBPK models are in need of "better methods or implementation, and the characterization of uncertainty and variability in PBPK models is not yet a sufficiently standard practice."[5] Such level of uncertainty and variability in PBPK modeling is not reliable as opposed to the sound science and robust weight of evidence provided in the available toxicological and epidemiological studies that IRIS relied upon for the Toxicological Review of Chloroprene (2010).[6]

The Toxicological Review of Chloroprene (2010) evaluated the evidence base of dozens of relevant studies – including epidemiological, toxicological, and mechanistic studies – and concluded that chloroprene is "likely carcinogenic to humans" via a mutagenic mode of action following inhalation exposure.[7] Evidence from occupational studies and toxicological studies showed an increased risk of liver cancer and lung cancer among workers, while animal studies revealed multi-tumor sites, including "tumors of the lung (bronchiolar/alveolar adenomas and carcinomas), forestomach, Harderian gland (adenomas and carcinomas), kidney (adenomas), skin and mesentery, mammary gland and liver…" - all of which was used to estimate the inhalation unit risk (IUR).[8] Notably, IRIS determined that it was appropriate to apply age-dependent adjustment factors to account for early-life susceptibility that cause increased lifetime cancer risk.[9] IRIS's evidence and conclusions are directly supported by or consistent with findings of similarly highly regarded, scientific agencies, like the National Toxicology Program (NTP) and the International Agency for Research on Cancer (IARC), which conclude that based on available evidence chloroprene is classified as "reasonably anticipated to be a human

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Supplemental Analysis of Metabolite Clearance, 85 Fed. Reg. 44,885 (July 24, 2020), https://www.regulations.gov/document?D=EPA-HQ-ORD-2020-0181-0001.

[4] EPA, Background Description for Chloroprene PBPK Modeling (July 2020), http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=540770.

[5] EPA, Uncertainty and Variability in Physiologically Based Pharmacokinetic Models: Key Issues and Case Studies, EPA/600/R-08/090 (August 2008), http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=477286.

[6] EPA, Toxicological Review of Chloroprene, EPA/635/R-09/010F (Sept 2010), https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/1021tr.pdf.

[7] *Id.*

[8] EPA, Response to Request for Correction 17002, Jennifer Orme-Zavaleta, PhD, NCEA, to Robert Holden, Denka (January 25, 2018), https://www.epa.gov/sites/production/files/2018-01/documents/epa_repsonse_to_mr._holdren_jan_25_2018_complete.pdf.

[9] *Id.*

carcinogen" (NTP) and it is "possibly carcinogenic to humans" (IARC).[10] The high standards set by each of these agencies results in chemical assessments that are both unbiased and reliable.[11]

Importantly, the IRIS chloroprene assessment underwent review by "internal science experts within EPA, by science reviewers from other federal agencies, and by the White House, and it was externally peer reviewed by independent experts including opportunity for public comment."[12] At the time of the review, "many of the topics and assertions raised by Denka Performance Elastomer (DPE) in the Request for Correction [(RfC)] were considered by agency and external peer reviewers during assessment development and external peer review because DuPont (the former owner of the La Place Louisiana facility that currently produces chloroprene) provided extensive comments during the public comment period."[13] According to EPA's response to the Request for Correction EPA evaluated DPE's claims that "the [chloroprene] IUR must be corrected by employing the PBPK model to sufficiently account for differences in mice and humans" and "concluded that the PBPK model available at the time of the assessment was inadequate for calculation of internal dose metrics or interspecies dosimetry extrapolations…"[14] As a part of its review for the Request for Correction, EPA carried out a systematic review of any studies published since the development of the IRIS chloroprene assessment.

In its Request for Correction, DPE claimed that studies published after the IRIS chloroprene assessment "address critical model validation issues identified at that time as a barrier to the application of a PBPK model."[15] EPA staff conducted a systematic review process with the purpose to "…evaluate human health-related studies of chloroprene published since the 2010 IRIS assessment to determine whether any new evidence is likely to have an impact on the current IRIS toxicity values…" EPA's systematic review process identified 182 studies published between the IRIS chloroprene assessment and DPE's Request for Correction – and systematically narrowed its review of relevant studies for analyzation to 7 – including the studies cited within DPE's Request for Correction.[16] EPA concluded that "the seven studies evaluated…represent novel approaches to analyzing existing epidemiologic, toxicological, and toxicokinetic data available for chloroprene. However, as is evident in the discussions of those studies, it is the opinion of EPA that these studies do not present sufficient evidence or provide adequate rationale for re-evaluating the entire chloroprene toxicity database. Ultimately, the Agency stands behind the conclusions made in the 2010 IRIS Toxicological Review of Chloroprene, including the derived cancer values. The new studies on chloroprene do not provide a reasonable basis for reassessing the human health effects due to chronic chloroprene

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[10] NTP, Report on Carcinogens, Fourteenth Edition – Chloroprene (2016), https://ntp.niehs.nih.gov/ntp/roc/content/profiles/chloroprene.pdf; IARC, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 71 – Chloroprene. https://monographs.iarc.fr/wp-content/uploads/2018/06/mono71-9.pdf.

[11] Similarly, California's Office of Environmental Health Hazard Assessment has long recognized chloroprene as a chemical "known to cause cancer." https://oehha.ca.gov/proposition-65/crnr/chloroprene-cobalt-sulfate-heptahydrate-and-fenoxycarb-listed-known-cause-cancer (listing chloroprene as a carcinogen in June 2000).

[12] EPA (January 25, 2018), *supra* note 8.

[13] *Id.*

[14] *Id.*

[15] *Id.*

[16] *Id,* (Attachment 2).

exposure."[17] To date, Commenters are aware of the single study, published by Clewell et al. (2019), which claims the chloroprene assessment overstated the carcinogenic potency IUR by a factor of 137, and serves as the basis for the Ramboll (2020) report submitted to EPA for review.[18] Commenters are concerned that EPA is questioning the science used to derive the chloroprene risk value on the basis of a single study, commissioned by the sole regulated entity in the U.S.

In EPA's 2018 response to the Request for Correction – EPA after nearly seven months of review – rightly concluded that "the underlying information and conclusions presented in the Toxicological Review of Chloroprene (CAS No. 126-99-8) In Support of Summary Information on the Integrated Risk Information System (IRIS) are consistent with the EPA's Information Quality Guidelines."[19] The response outlined and provided rationale for the Agency's decision by addressing each of the issues raised by Denka in its Request for Correction. Notably, EPA addressed a key issue regarding the use of PBPK modeling – that "the IUR must be corrected by employing the PBPK model to sufficiently account for differences in mice and humans."[20]

In 2018 – after nearly seven months of review – EPA issued a denial to DPE's Request for Correction and rightly concluded that the underlying review was consistent with EPA's Information Quality Guidelines (IQR).[21] On July 19, 2018 (only days before DPE submitted its Request for Reconsideration), EPA staff met with officials from the Louisiana Department of Environmental Quality, Denka, and Ramboll (a consulting group hired by Denka) to discuss a newly developed physiologically based pharmacokinetic (PBPK) model by Ramboll that resulted in a cancer-risk estimate far less stringent than the IRIS assessment derived.[22] At the time, the PBPK model had not undergone an independent peer review process. Since 2018, EPA has met with Ramboll numerous times according to EPA's public record tracker.[23]

On July 24, 2018, Denka sent a letter to EPA suggesting that particular EPA staff (*i.e.*, Paul Schlosser) would be "go[ing] over the model," and stating that Denka was "pleased to hear that EPA intends to give high priority to the PBPK model evaluation and we look forward to receiving an updated timeline for the evaluation process."[24] During the meeting, it appears that Denka believed EPA agreed to review the draft model, suggest improvements and upon revision, and arrange for some kind of additional review of the model.

On April 23, 2020, Ramboll submitted a report to EPA, as commissioned by DPE – the sole regulated entity in the source category subject to EPA's Neoprene Production National

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[17] *Id.*

[18] Clewell, HJ et al. Incorporation of in vitro metabolism data and physiologically based pharmacokinetic modeling in a risk assessment for chloroprene (2019). Inhal Toxicol 31: 468-483. http://dx.doi.org/10.1080/08958378.2020.1715513.

[19] EPA (January 25, 2018), *supra* note 8.

[20] *Id.*

[21] *Id.*

[22] Summary of Meeting Action Items, Event Title: Chloroprene Request for Correction/Request for Reconsideration (July 19, 2018), https://cfpub.epa.gov/ncea/iris2/event_attachment.cfm?layout=none&attach_id=544.

[23] EPA. Meetings Requested by Specific Members of the Public (March 13, 2015). https://cfpub.epa.gov/ncea/iris2/events.cfm#stakeholderMeetings.

[24] Letter from Patrick A. Walsh, Denka, to John Vandenberg, PhD, NCEA (July 24, 2018), attached as Attachment 1.

Emission Standards for Hazardous Air Pollutants,[25] which operates a facility in Laplace Louisiana. Commenters reviewed documented active and archived Request for Correction and Request for Reconsideration actions on prior chemicals. It appears that the current actions pursued by EPA are out of step with previous actions undertaken by the agency.

Furthermore, the current action does not appear to be aligned with the EPA *Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility and Integrity of Information Disseminated by the Environmental Protection Agency,* also known as the Information Quality Guidelines *(IQG)*. Importantly, the IQR defines the term objectivity as the "…focus on whether the disseminated information is being presented in an accurate, clear, complete, and unbiased manner, and as a matter of substance, is accurate, reliable and unbiased."[26] The IQR goes on to state that "for purposes of these Guidelines, EPA disseminates information to the public when EPA initiates or sponsors the distribution of information to the public," which includes "Agency-sponsored distribution…where EPA reviews and comments on information distributed by an outside party in a manner that indicates EPA is endorsing it…"[27] EPA states the purpose of its current external review of the Ramboll (2020) PBPK model is "for possible use in updating the 2010 Integrated Risk Information System (IRIS) Toxicological Review of Chloroprene."[28] It goes on to state, "the focus and ultimate objective of this peer review is to assist in EPA's determination of whether the model is of sufficient scientific quality and reliability to support consideration in an IRIS human health assessment."[29]

EPA scientists and staff have worked with DPE/Ramboll as the company developed an updated PBPK model, culminating in the 2020 Ramboll Report.[30] EPA's current actions in response to DPE's Request for Reconsideration appear to be non-objective and infected with bias for the regulated industry. Commenters are unaware of any action, current or archived, that the IRIS program has undertaken that is similar to the process for the Request for Reconsideration (case #17002A).

Critique of Ramboll (2020) report & EPA Uncertainty Analysis

A 2019 study published in the *Journal of Toxicological Sciences* describes the difficulties with applying PBPK models for use in public health decision making.[31] Researchers from EPA, the Agency for Toxic Substances and Disease Registry (ATSDR), and the U.S. Food and Drug Administration sought to objectively evaluate and review known challenges with the application of PBPK models in decision making, specifically because of "lack of confidence in PBPK

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[25] 40 C.F.R. Part 62 Subpart U (40 C.F.R. Sec. 63.480-506).
[26] EPA. Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility and Integrity of Information Disseminated by the Environmental Protection Agency (October 2002), https://www.epa.gov/sites/production/files/2020-02/documents/epa-info-quality-guidelines_pdf_version.pdf.
[27] *Id.*
[28] EPA (July 2020), *supra* note 4.
[29] *Id.*
[30] Ramboll. Incorporation of in vitro metabolism data in a physiologically based pharmacokinetic (PBPK) model for chloroprene (April 2020), http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=540598.
[31] Tan, Y. et al. Challenges Associated With Applying Physiologically Based Pharmacokinetic Modeling for Public Health Decision-Making (2018), Toxicological Sciences, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6084449/.

models for which no tissue/plasma concentration data exist for model evaluation."[32] Researchers reviewed the Federal Register (FR) to identify federal actions involving PBPK modelling by using specific search terms including "PBPK" and "proposed rules, rules, and supporting materials."[33] The review goes on to acknowledge that, "[s]everal FR documents alluded to PBPK modeling in the context of precluding its use in risk assessment due to the limitations and uncertainties perceived or inherent in model development and/or application. For example, a FR document issued by the EPA concluded that a published PBPK model for perchlorate cannot be used when establishing a maximum contaminant level in drinking water due to issues such as inconsistencies in model code, lack of inclusion of a sensitive population, and uncertainties in animal-to-human extrapolation (FR, 2016a). Reasons listed in this example along with other reasons, such as low confidence in a model's capability to characterize intra-species variability or to extrapolate to conditions in which no data exist for evaluation, represent some common concerns raised by risk assessors."[34] Commenters agree that the application of PBPK models in regulatory decision-making requires additional scrutiny given the magnitude of potential limitations and uncertainties associated with these models and the necessity for applicability to the general public.

The review also revealed that the EPA is one of the agencies with what researchers found to be the most PBPK-related FR entries. Due this finding, the review went on to evaluate how the use of PBPK modeling was applied (or not applied) in IRIS risk assessments. The use of PBPK modeling within published IRIS assessments was found to be rather limited with only about 10% of available documents referencing PBPK modeling, and only 1.8% utilizing "PBPK models to derive reference dose and/or reference concentration values (e.g. for trichloroethylene, methanol, vinyl chloride)."[35] The review of the IRIS database also revealed that chief challenges that precluded the application of PBPK modeling to the derivation of a unit risk estimate included "inadequate model structure or parameterization for proper route-to-route or interspecies extrapolation, inadequate description of the pharmacokinetics of active metabolites, and lack of human time-concentration data necessary for model evaluation."[36] As described above, the Ramboll (2020) PBPK model could potentially be among just <2% of PBPK models to be applied in an IRIS human health assessment. Yet, Commenters have identified a number of challenges and shortcomings that undermine the reliability and validity of the Ramboll (2020) PBPK model. Given the known challenges with applying a PBPK model for decision-making purposes, Commenters urge the external review panel to thoroughly evaluate the limitations of the Ramboll (2020) PBPK model, taking into account the flaws and deficiencies of the proposed model for applying to human health risk assessment.

EPA's *Supplement: Uncertainty Analysis of In Vitro Metabolic Parameters and of in In Vivo Extrapolation (IVIVE) Used in a Physiologically Based Pharmacokinetic (PBPK) Model for Chloroprene* (July 2020) acknowledges that the Ramboll (2020) report did not "…estimate

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[32] *Id.*
[33] *Id.*
[34] *Id.*
[35] *Id.*
[36] *Id.*

the quantitative uncertainty in the PBPK model."[37] It goes on to state that from EPA's own analysis of uncertainty, "[i]initial results from the uncertainty analysis indicate that the overall uncertainty range in some parameters may differ from the 95% confidence interval estimated for the mean value reported by Ramboll (2020)."[38] Commenters cannot overstate the importance of quantifying *all* areas of uncertainty as well as the challenges associated with characterizing uncertainty and variability for PBPK models. EPA's National Center for Environmental Assessment has published on the aforementioned challenges and notes that importantly, PBPK models are "designed to determine the relationship between external exposure and biologically-relevant (usually internal) dose, and their predictions can be used for extrapolating across routes, levels, or patterns of exposure, and for quantitatively characterizing differences in susceptibility across species, populations, and life-stages."[39] Yet, the Ramboll (2020) report did not even attempt to characterize (or quantify) the uncertainty and variability that might affect susceptible populations or life-stages.

EPA's supplemental uncertainty analysis quantifies a number of additional uncertainties, for review by the forthcoming peer review panel. Importantly, EPA *identified* an uncertainty with respect to the assumption that "the rate of oxidative metabolism per mg microsomal protein observed in vitro equals the rate of oxidative metabolism per mg protein in the endoplasmic reticulum that occurs in vivo. Additionally, only single pooled samples of tissue/species specific microsomes were procured. The degree to which these samples represent population average metabolic rate is an additional uncertainty. The U.S. EPA has not identified appropriate information sources to quantify this uncertainty."[40] As previously stated, PBPK models can be used to "extrapolate across species, life stages, exposure routes and timing."[41] A key consideration Commenters raise is for external reviewers to identify the ability for the PBPK model to characterize intra-species variability, which may help account for impacts across different life stages in human development. EPA's uncertainty analysis appears to downplay the importance of considering inter-species variability stating, "the objective of cancer risk assessment is to identify the average cancer risk in the population. Therefore, the focus of the uncertainty analysis described here is on the uncertainty in the IVIVE calculations for humans, rather than estimating inter-individual variability that derives from variation in all physiological parameters among the population. Hence, only the impact of uncertainty in the physiological parameters directly involved in the IVIVE calculations will be evaluated."[42] Commenters are concerned that this limiting in scope arbitrarily discounts the importance of inter-individual variability among the general population. In a meeting with scientists held by EPA, consensus was reached that "[E]ven within probabilistic analyses, questions remain as to what percentiles of uncertainty and variability to use, as well as how to evaluate whether the estimates of human variability are representative of the full human population taking into account susceptible populations and life-stages. Therefore, work remains to be done on methods and approaches to

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[37] EPA. Supplement: Uncertainty Analysis of In Vitro Metabolic Parameters and of In Vitro to In Vivo Extrapolation (IVIVE) Used in a Physiologically Based Pharmacokinetic (PBPK) Model for Chloroprene (July 2020), http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=540771.
[38] *Id.*
[39] EPA (August 2008), *supra* note 5.
[40] EPA (July 2020), *supra* note 36.
[41] Tan, Y et al. (2018), *supra* note 30.
[42] *Id.* Here, IVIVE stands for in vitro to in vivo extrapolation.

integrating estimates of pharmacokinetic (and other sources of) uncertainty and variability into risk assessment."[43]

In its 2020 Report, Ramboll cites Allen et al. (2014) as an authoritative source in its discussion of the selection process for its dose metric compares the EPA vinyl chloride PBPK model stating:

> The use of a PBPK model to estimate target tissue dose…was able to produce similar human risk estimates using data from animal bioassays and human occupational exposures. As a similar test of the chloroprene PBPK model to support cross-species estimates obtained using external (air concentration) and internal (PBPK model estimated) metrics for the female mouse bioassay and human occupational exposures. The analysis concluded that if inhaled concentration was used as the dose metric, the estimated of human cancer risk using animal and human data were statistically significantly different, whereas using the PBPK metric consistent risk estimates were obtained across species. As with vinyl chloride, the use of the PBPK-based metric effectively reconciled the differences in mouse and human low-dose risk estimates.[44]

Notably, EPA, in its 2018 Response to the Request for Correction outlines several major issues with the Allen et al. (2014)[45], stating, "[t]he difference between female mice and humans (female mice/human value) was 7.4, 4.8, and 2.5 at those same doses. The subsequent dose-response analysis by Allen et al. (2014) only incorporates female mouse data, and no rationale for the omission of male mouse data are provided. It cannot be determined whether this discrepancy reflects on the usability or validity of the model because it is possible that site-specific metabolism truly differs substantially between male mice and female mice. However, the discrepancy indicates that the site-specific dose metric may not be appropriate for dose-response modeling and animal-to-human extrapolation."[46] EPA goes on to evaluate the Allen et al. (2014) study for its potential impact on the updated chloroprene literature base. Here, EPA notes additional issues with the study, including the use of an external comparison population (as opposed to the conventional use of internal controls as "more valid and relevant given concerns including biases such as the healthy worker and healthy worker survivor effects."[47] The effect of which EPA concludes, "likely underestimated the magnitude of human responses."[48] EPA goes on to list other ways the Allen et al. (2014) analysis is inadequate for dose-estimation and ultimately concludes, "[t]he combined dose-response analysis (Allen et al., 2014) relied on judgements that underestimated risk in female mice and particularly underestimated human risk, given existing data."[49]

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[43] EPA (August 2008, *supra* note 5.
[44] Ramboll (April 2020), *supra* note 30.
[45] *See* Allen, B et al. A constrained maximum likelihood approach to evaluate the impact of dose metric on cancer risk assessment: application to β-chloroprene (2014). Regul. Toxicol. Pharmacol. 70: 203-213. http://dx.doi.org/10.1016/j.yrtph.2014.07.001.
[46] EPA (January 25, 2018), *supra* note 8.
[47] *Id.*
[48] *Id.*
[49] *Id.*

Importantly, the systematic review of updated chloroprene studies resulted in "the Agency stand[ing] behind the conclusions made in the 2010 IRIS Toxicological Review of Chloroprene, including the derived cancer values. The new studies on chloroprene do not provide a reasonable basis for reassessing the human health effects due to chronic chloroprene exposure."[50] Thus, Commenters are also concerned that other studies and sources cited by Ramboll (2020) (e.g. Thomas et al. (2013)[51]) may require further inspection by the external peer review panel to ensure assertions made within the report are relevant, accurate and do not overstate or mischaracterize the findings of referenced studies

Finally, scientists who attended the 2019 meeting with IRIS submitted a public comment in response to EPA's current action outlining a number of criticisms with respect to the Ramboll (2020) report and accompanying Clewell (2019) paper.[52] The comment (submitted by Kaltofen et al. (2020)) identified a "fundamental flaw in the proposed Ramboll (2020) PBPK model" regarding the "…explicit assumption that chloroprene metabolite clearance [in the lung tissues] would be identical for mice and humans, citing the case of methylene chloride as an example. While the authors speculate the mechanism underlying a clearance pathway, they present no evidence to support their speculation."[53] The comment goes on to state:

> "As compared to Clewell et al. (2019)'s use of methylene chloride as the basis for assumptions about comparable clearance rates between mice and humans, the case of ethylene oxide, the simplest epoxide that is analogous to the epoxide metabolites of chloroprene, likely serves as a more appropriate analog for the differential behavior of chloroprene metabolites across species. Research has shown that mice eliminate ethylene oxide at a rate more than an order of magnitude faster than humans (Filser & Klein 2018). Such a difference suggests that each unit of chloroprene metabolite generated in a tissue spends a significantly longer time in the human body as compared to the mouse, indicating the potential for an overall greater presence of the compound in humans. This translates to an increase in the availability of the reactive epoxide metabolites to interact with DNA in target tissues."[54]

According to the comment, the consequence of the assumption of "identical clearance rates of chloroprene in mice and humans" would lead to an underestimation of risk to humans.[55] Commenters are highly concerned about the significance of the error identified by Kaltofen et al. (2020) and urge the peer review panel to investigate each critique raised in the comment to the fullest extent -- and recognize that EPA should not revisit, and should instead take action to protect public health based upon, the 2010 IRIS value for chloroprene.

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[50] EPA (January 25, 2018), *supra* note 8.

[51] Thomas, R. Cross-species transcriptomic analysis of mouse and rat lung exposed to chloroprene (2013). Toxicol Sci 131: 629-640. http://dx.doi.org/10.1093/toxsci/kfs314.

[52] Kaltofen, M. et al. Public comments in response to EPA's external peer review of a Report on Physiologically Based Pharmacokinetic (PBPK) Modeling for Chloroprene (Ramboll, 2020) and a Supplemental Analysis of Metabolite Clearance (U.S. EPA, 2020) (2020), https://www.regulations.gov/document?D=EPA-HQ-ORD-2020-0181-0012.

[53] *Id.*

[54] *Id.*

[55] *Id.*

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The community members living near the Denka facility are dealing with real-world impacts from exposure to chloroprene – that is documented in the *Waiting to Die* report[56] and as recognized by EPA's NATA data.[57] The Ramboll (2020) report should not be the sole source of reliance for reevaluating the IRIS chloroprene assessment when the 2010 chloroprene risk value is based on the best available science. Furthermore, the DPE Request for Reconsideration has been unresolved for over two years. EPA's IQG state: "EPA's goal is to respond to each RFR within 90 days of receipt, by 1) providing either a decision on the request or 2) if the request requires more than 90 calendar days to resolve, informing the complainant that more time is required and indicate the reason why and an estimated decision date."[58] EPA should dismiss DPE's Request for Reconsideration and dismiss the Ramboll (2020) PBPK model given the magnitude of uncertainty inherent in the model and the critical issues with the model and approach.

Rather than continuing an endless cycle of inappropriate and unnecessary reconsideration – which is what EPA appears to be stuck in – EPA must take immediate action, finally, to protect the community members exposed to Denka's chloroprene emissions. Further, instead of weakening the air monitoring to use what appears to be a method not validated by EPA and that will fail to measure many chloroprene emissions as EPA has proposed, EPA must maintain the continuous air monitoring using Method TO-15,[59] and supplement this with optical remote sensing to ensure the most up-to-date real-time information on the pollution crossing the fenceline.[60]

In addition to protecting the community's right to know how much chloroprene is coming into their neighborhood, backyards, schoolyards, and playgrounds, without any further delay EPA must exercise its full authority to reduce Denka's chloroprene emissions so that ambient concentrations in the neighborhood from this facility finally fall *below* the 2010 IRIS value. EPA has no excuse for refusing to protect public health, and the double dangers of COVID-19 and air pollution only highlight the injustice of EPA's failures—especially in a community also exposed to other sources of toxic air, including ethylene oxide, where the cumulative toxic impact is well-understood to be overwhelming and unbearable.[61] After years of knowing that community

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[56] Waiting to Die: Toxic Emissions and Disease Near the Louisiana Denka / DuPont Plant, Univ. Network for Human Rights (July 2019), https://www.epa.gov/sites/production/files/2019-12/documents/waiting_to_die_final.pdf.

[57] EPA (2018), *supra* note 2.

[58] EPA (October 2002), *supra* note 26.

[59] EPA, Ambient Air Sampling/Monitoring Plan for Chloroprene in the Area Near Denka Performance Elastomer Pontchartrain Facility, LaPlace, Louisiana (May 2016), https://www.epa.gov/sites/production/files/2016-07/documents/final_ambient_air_monitoring_plan_for_dpe_laplace_la_may_2016.pdf; EPA Method TO-15, https://www.epa.gov/quality/analysis-volatile-organic-compounds-air-contained-canisters-method-15-sop-no-hw-31-revision.

[60] EPA Handbook, Optical Remote Sensing for Measurement and Monitoring of Emissions Flux (Dec. 2011), https://www3.epa.gov/ttn/emc/guidlnd/gd-052.pdf

[61] Terrell, K. & James, W. Air Pollution and COVID-19: A Double Whammy for African American and Impoverished Communities in Cancer Alley (2020), https://law.tulane.edu/sites/law.tulane.edu/files/Files/Terrell%20-%20COVID-19%20-%20PM%202.5%20Louisiana%202020-5-14%20WEB%20VERSION.pdf; Sneath, S. Louisiana's river region

members are exposed to unacceptable levels of this cancer-causing pollutant, EPA's inaction shocks the conscience and has led to a generation of children facing cancer and other health threats that no one would face from air pollution if EPA were simply doing its job. Instead of continuing this cycle of reconsideration without any valid scientific basis, we call for EPA to take action to finally protect the health of the community exposed for far too long to chloroprene pollution.

Please contact us if you would like additional information or to discuss what action EPA will take to prevent more cancer and early mortality linked to air pollution in the community exposed to Denka's pollution.

Sincerely,

Mary Hampton
President
Robert Taylor
Executive Director
Concerned Citizens of St. John
985-210-1976 or 504-559-7304
hamptonmaryc@gmail.com
btcnola@gmail.com

Michelle Mabson, MPH, MSc
Staff Scientist
Emma Cheuse
Staff Attorney
Earthjustice
1001 G Street, NW Suite 1000
Washington, DC 20001
Office: 202-667-4500 ext. 5254 or 5220
mmabson@earthjustice.org
echeuse@earthjustice.org

Ruhan Nagra
Supervisor in Human Rights Practice
University Network for Human Rights
77 Pearl Street
Middletown, CT 06457
314-435-2377
ruhan@humanrightsnetwork.org

Wilma Subra
Chemist / Technical Director
Louisiana Environmental Action Network
(225) 928-1315

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